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ABOUT COVER

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ORIGINAL ARTICLE

Prospective Study

Immunoprophylaxis failure and vaccine response in infants born to mothers with chronic hepatitis B infection in Djibouti

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Abstract

BACKGROUND

In endemic areas, vertical transmission of hepatitis B virus (HBV) remains a major source of the global reservoir of infected people. Eliminating mother-to-child transmission (MTCT) of HBV is at the heart of World Health Organization's goal of reducing the incidence of HBV in children to less than 0.1% by 2030. Universal screening for hepatitis B during pregnancy and neonatal vaccination are the main preventive measures.

AIM
To evaluate the efficacy of HBV vaccination combined with one dose of immunoglobulin in children born to hepatitis B surface antigen (HBsAg)-positive mothers in Djibouti city.

METHODS
We conducted a study in a prospective cohort of HBsAg-positive pregnant women and their infants. The study ran from January 2021 to May 2022, and infants were followed up to 7 mo of age. HBV serological markers and viral load in pregnant women were measured using aVidas microparticle enzyme-linked immunosorbent assay (Biomérieux, Paris, France) and the automated Amplix platform (Biosynex, Strasbourg, France). All infants received hepatitis B immunoglobulin and were vaccinated against HBV at birth. These infants were closely monitored to assess their seroprotective response and for failure of immunoprophylaxis. Simple logistic regression was also used to identify risk factors associated with immunoprophylaxis failure and poor vaccine response. All statistical analyses were performed with version 4.0.1 of the R software.

RESULTS
Of the 50 pregnant women recruited, the median age was 31 years, ranging from 18 years to 41 years. The MTCT rate in this cohort was 4% (2/50) in HBsAg-positive women and 67% (2/3) in hepatitis B e antigen-positive women with a viral load > 200000 IU/mL. Of the 48 infants who did not fail immunoprophylaxis, 8 (16%) became poor responders (anti-HB < 100 mIU/mL) after HBV vaccination and hepatitis B immunoglobulin, while 40 (84%) infants achieved a good level of seroprotection (anti-HB > 100 mIU/mL). Factors associated with this failure of immunoprophylaxis were maternal HBV DNA levels (> 200000 IU/mL) and hepatitis B e antigen-positive status (odds ratio = 158, 95% confidence interval: 5.05-4958, $P < 0.01$). Birth weight < 2500 g was associated with a poor immune response to vaccination (odds ratio = 34, 95% confidence interval: 3.01-383.86, $P < 0.01$).

CONCLUSION
Despite a failure rate of immunoprophylaxis higher than the World Health Organization target, this study showed that the combination of immunoglobulin and HBV vaccine was effective in preventing MTCT of HBV. Therefore, further studies are needed to better understand the challenges associated with immunoprophylaxis failure in infants in Djibouti city.

Key Words: Hepatitis B surface antigen; Infants; Hepatitis B immunoglobulin; Hepatitis vaccine; Djibouti

Core Tip: This study evaluated the effectiveness of hepatitis B virus (HBV) vaccination and immunoglobulin administration in infants born to hepatitis B surface antigen-positive mothers. The mother-to-child transmission rate was 4%, increasing to 67% in hepatitis B e antigen (HBeAg)-positive women with a viral load > 200000 IU/mL. A seroprotective response was achieved in 84% of infants, and immunoprophylaxis failure was associated with maternal HBV DNA levels and positive HBeAg status. This combination has been shown to be effective in preventing HBV mother-to-child transmission in HBeAg-negative women and demonstrated the value of peripartum prophylaxis for women at risk.

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INTRODUCTION

Hepatitis B virus (HBV) is a major public health problem affecting approximately 2 billion people worldwide, with 296 million chronically infected, including 6 million children under 5-years-old[1,2]. Mother-to-child transmission (MTCT) is the major mode of HBV transmission in endemic areas. Without preventive measures, 70%-90% of HBV-infected mothers will transmit HBV to their infants, and 90% of these infants will be at high risk of developing chronic hepatitis B, which can lead to cirrhosis and hepatocellular cancer in adulthood[3,4]. In highly endemic areas such as sub-Saharan Africa (SSA), MTCT accounts for approximately 50% of new infections, compared to 30% in low endemic areas[5]. Therefore, the cornerstone of the global strategy to eliminate viral hepatitis by 2030 is the prevention of MTCT[6].

The most important prevention measures are antenatal screening for HBV, postpartum prophylaxis for mothers at high risk, and the universal introduction of the hepatitis B vaccine[7]. In 2009, the World Health Organization (WHO) recommended that all countries in the world vaccinate infants using three or four doses of the HBV vaccine, with the first

dose administered within 24 h of birth[8,9]. African countries have progressively introduced the hepatitis B vaccine into their Expanded Programme on Immunization (EPI) since the 1990s. To date, all countries have introduced a two or three doses series (Hep B3) using a pentavalent or hexavalent vaccine programmed at 6 wk, 10 wk, and 14 wk[10]. However, only 14/47 countries offered the WHO-recommended monovalent Hepatitis B Birth Dose (Hep B-BD) vaccine administered within the first 24 h[11]. This strategy should be complemented by the administration of hepatitis B immunoglobulin (HBIG) at birth. However, this is not currently feasible in SSA due to concerns about the cost and availability of HBIG[11].

Despite the existence of the vaccine, the failure rate of immunoprophylaxis in infants born to hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg)-positive mothers is 5%-10%[12]. A systematic review in 2023 described a failure rate of 6.5% in SSA. The main confounding factors were maternal HBV DNA viral load and HBeAg positivity, although other studies have identified other non-constant factors such as infant weight, mode of delivery, and vaccination schedule, with some countries starting the first dose at 6 wk of age[13,14].

In Djibouti, data on HBV infection are very limited, with studies conducted among blood donors in 1986 and 2005 reporting a prevalence of 7% and 10%, respectively. A recent study reported a prevalence of 9% in pregnant women in 2023[15-17]. Vaccinating against HBV (Hep-B3) has been included in the EPI since 2008, supported by the Global Alliance for Vaccines. The monovalent Hep B-BD vaccine was introduced in 2012. Djibouti also does not perform post vaccination serological testing (PVST) for infants born to HBsAg-positive mothers, and this lack of surveillance makes it difficult to assess high-risk infants. In the present study, we conducted a prospective study of a cohort of HBsAg-positive mothers and their infants to assess the protective efficacy of an immunoprophylaxis protocol combining HBV vaccine + HBIG and to evaluate vaccine response by PVST.

MATERIALS AND METHODS

Study population recruitment

We conducted a multicenter prospective cohort study in the city of Djibouti (Republic of Djibouti) between January 2021 and May 2022 to assess whether early administration of HBIG and hepatitis B vaccine at birth (within 1 h of birth) in infants born to HBV-infected mothers can further increase the protective efficacy of current immunoprophylaxis. Nine antenatal care centers, geographically located in the southern, central, and northern regions of the city of Djibouti, participated in the study. Pregnant women who tested positive for HBsAg in the antenatal clinics were invited to participate in the study on a voluntary basis after a detailed explanation. The inclusion criteria were: Pregnancy; above 18-years-old; confirmation of HBsAg positivity; and willingness to bring the unborn child for the planned follow-up visits at about 6 mo postpartum. An informed consent form was signed, and a questionnaire completed. The interview with the mother was scheduled at the time of enrolment.

Within the first 24 h of life, neonates received HBIG 200 IU (HEPATITIS B-IG Behring 200 IU CSL Behring AG) and one dose of monovalent hepatitis B vaccine (Hep B-BD). The infants were further vaccinated with a pentavalent vaccine (Hep B3) at 6 wk, 10 wk, and 14 wk of age, in accordance with national recommendations for maternal and child health. Children born to HBsAg-positive mothers were seen at birth and at 7 mo of age. Their clinical course and infection status were assessed.

Data collection

When the mothers visited the polyclinics, the principal investigator was responsible for completing the standardized questionnaires. The questionnaires were administered in person and the following sections were covered: Sociodemographic data; weeks of pregnancy; family history of hepatitis B; antiviral treatment; and whether they were aware of the HBV infection. Mothers were followed up by telephone after delivery, including mode of delivery, infant sex, infant weight, gestational age, and HBV vaccine dose at the time of injection. In addition, infants were followed up three times after birth (24 h, 1 mo, and 6 mo) to obtain information on HBV vaccination, and HBV serological markers were measured at 7 mo of age.

Biological analysis

All pregnant women were screened for hepatitis B markers using a rapid diagnostic test, the ACON® HBsAg Rapid Test (T&C Beheer BV, China). For women who tested positive, a 5-6 mL EDTA-blood sample was taken. The plasma was separated by centrifugation, and aliquots were stored at -30 °C. Plasma samples were serologically tested for hepatitis B markers, including HBsAg, HBs antibodies, HBeAg, HBe antibodies, and hepatitis B core antibodies, using a microparticle enzyme-linked immunosorbent assay (Vidas; Biomerieux, Paris, France) at the Caisse National de Securite Social laboratory. HBV DNA viral load in infected patients was quantified by real-time PCR using the Amplix automated platform (Biosynex, Strasbourg, France). The detection threshold for this instrument was set at 26 copies/mL.

PVST for hepatitis B was performed in children at 7 mo of age. HBsAg-positive infants were considered to have failed immunoprophylaxis and to have HBV infection. The vaccine response was assessed by the level of HBs antibodies at the end of the vaccination regimen with: (1) No response if HBs antibody level was < 10 mUI/mL; (2) Poor response if HBs antibody level was between 10 and 100 mIU/mL; and (3) Good response when HBs antibody level was ≥ 100 mIU/mL. The study design is presented in Figure 1.

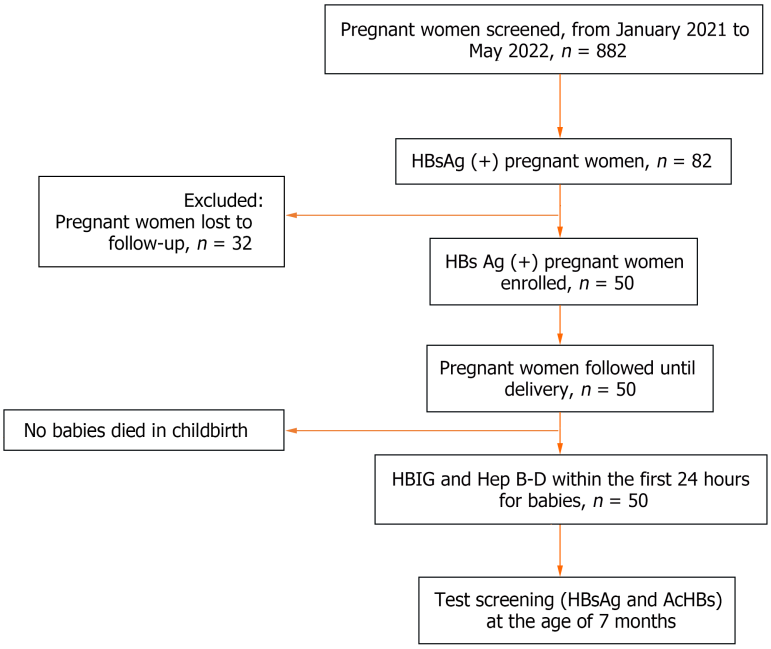

Figure 1 Diagram of study design for hepatitis B surface antigen-positive pregnant women and their infants. AcHBs: Hepatitis B surface antibody; HBIG: Hepatitis B immunoglobulin; HBsAg: Hepatitis B surface antigen; Hep B-BD: Hepatitis B Birth Dose.

Statistical analysis

Data from the questionnaire were entered into the Care Center Entry database. Variables of interest included infant status and vaccine response. Secondary variables included the mother's sociodemographic, clinical, and biological factors associated with infant infection. Descriptive analysis was performed to examine the distribution of frequencies and variabilities.

χ^2 or Fisher exact tests were used for categorical variables. Simple logistic regression was also used to identify risk factors associated with immunoprophylaxis failure and poor vaccine response. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to estimate risks, and a P value of less than 0.05 was considered significant. All statistical analyses were performed with R software version 4.0.1.

Ethical considerations

The study was approved by the Scientific Committee of the Ministry of Health of the Republic of Djibouti under N0 149/DG/INSPD/2023. Participants were informed of the purpose of the study and their right to confidentiality. Informed consent was obtained from each participant.

RESULTS

Characteristics of pregnant women

From January 2021 to May 2022, 882 pregnant women were screened, and 82 tested positive for HBsAg. Only 50 were recruited for this study, and the 32 pregnant women who were lost to follow-up had the following reasons for dropping out: Distance from the hospital; moving to a neighboring country; and fear of family stigma. The characteristics of the pregnant women and their infants are summarized in Table 1. Out of the 50 pregnant women recruited, the median age was 31 years, with a minimum of 18 years and a maximum of 41 years. Forty-two women (84%) were aged between 20 years and 40 years, and 38% (n = 19) and 44% (n = 22) were unemployed and illiterate, respectively.

All the pregnant women were monitored by a health worker, and 62% (n = 31) were multiparous. They were all married, and 68% (n = 34) of pregnant women were examined after the first trimester. About one-third of the pregnant women had received a blood transfusion (28%, n = 14), had a family history of HBV (34%, n = 17), or had a history of abortion (30%, n = 15). Biological analyses of HBV-DNA viral load and serological markers of HBV virus were available for all patients. Three (6%) mothers had a viral load superior to 200000 IU/mL and were positive for HBeAg.

Characteristics of infants

The majority of infants were born *via* cesarean (78%, n = 39) and weighed between 2500-3500 g (72%, n = 36). Thirty-two (64%) of the neonates were males giving a sex-ratio (male/female) of 1.8. Two infants (2/50) were positive for HBsAg, yielding an MTCT rate of 4% in this cohort. The two infants who failed immunoprophylaxis were born from mothers with a viral load > 200000 IU/mL (2/3) and positive for HBeAg (2/3).

Table 1 Sociodemographic characteristics of the hepatitis B surface antigen-positive pregnant women, *n* = 50

Variables	Frequency	%
Age of mother in yr, *n* = 46		
18-20	1	2
20-30	21	46
30-40	21	46
> 40	3	6
Mother occupation		
Employed	31	62
Unemployed	19	38
Mother education level		
Illiterate	22	44
Primary	5	10
Secondary	18	36
University	5	10
Parity		
Nulli or primiparous 0-1	7	14
Multiparous 1-3	31	62
Large multiparous	12	24
First antenatal care		
1 trimester	16	32
2 trimester	16	32
3 trimester	18	36
History of blood transfusion		
Yes	14	28
No	36	72
History of abortion		
Yes	15	30
No	35	70
Family history of HBV		
Yes	17	34
No	33	66
Vaccination against HBV		
Yes	0	0
No	50	100
Marital status of mother		
Married	50	100
Not married	0	0
Monitoring by a health care worker		
Yes	50	100
No	0	0
HBeAg status of mother		
Negative	47	94

Positive	3	4
Viral load HBV DNA		
< 200000	47	94
> 200000	3	6

HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus.

Of the 48 infants who did not fail immunoprophylaxis, 8 (16%) became poor responders (anti-HBs < 100 mIU/mL) after HBV vaccination and HBIG injection, while 40 (84%) infants achieved a good level of seroprotection (anti-HBs ≥ 100 mIU/mL), indicating that they were good responders. Table 2 summarizes the biological status and response to immunization of the infants.

Characteristics of HBV-infected infants and their mothers

The characteristics of the two infected infants and their mothers are summarized in Table 3. The two mothers were 32-years-old and 34-years-old, illiterate, and a family history of HBV and were diagnosed during the third trimester of pregnancy. Biological results showed a viral load > 200000 IU/mL and the presence of HBeAg. The two infants who failed immunoprophylaxis were born vaginally, were males, and weighed 2.5 kg and 3.5 kg.

Factors associated with HBV infection in infants

A bivariate analysis was performed to identify the factors associated with this immunoprophylaxis failure (Table 4). Maternal HBV DNA levels (> 200000 IU/mL) and HBeAg-positive status (χ^2 = 32.64; OR = 158; 95%CI: 5.05-4958; P < 0.01) were independently associated with an increased risk of immunoprophylaxis failure. Other factors, in particular mode of delivery, were not associated with HBV infection.

Factors associated with a low level of HBs antibody

Factors associated with a poor response to immunoprophylaxis were assessed using bivariate analysis. Only infant birth weight < 2500 g was associated with a low immune response to vaccination (χ^2 = 17.97, OR = 34; 95%CI: 3.01-383.86, P < 0.01) (Table 5).

DISCUSSION

Our prospective analysis was designed to assess the rate of perinatal HBV transmission as well as the vaccine response of infants. From January 2021 to May 2022, a cohort of 50 HBsAg-positive pregnant women and their infants were followed. A total of 50 mother-infant pairs were monitored at the Care Center 1 in Djibouti city. Indeed, of the 82 patients who tested positive, 32 were lost to follow-up. The main reasons were stigmatization within their households and the lack of proximity between the specialized centers and their homes.

Patients were lost between the medical laboratory, the gastroenterologist, and the prenatal care service. This suggests the need to adopt a public health approach using simplified service delivery, screening, and treatment. Treatment should be decentralized to peripheral health facilities, while cases of advanced hepatopathy requiring advanced clinical support should be referred to specialized centers. Other patients refused to continue the study because of fear of social stigma and self-stigma, negative beliefs about HBV transmission, or lack of knowledge about transmission routes (some thought HBV could be transmitted by sharing food).

Seroprevalence of hepatitis B MTCT

In this cohort, infants born to HBsAg-positive mothers received an identical vaccination schedule consisting of Hep B-BD combined with HBIG within the first 24 h, followed by 3 doses of Hep B3 (at 6 wk, 10 wk, and 14 wk of age). However, despite this appropriate post-exposure prophylaxis, some infants became infected, with an immunoprophylaxis failure rate of 4% rate (2/50). None of the infants born to HBeAg-negative mothers became infected with HBV.

Higher MTCT rates for hepatitis B have been reported in several studies in Africa, particularly in Ethiopia (30.9%), Angola (22.0%), and Libya (60.9%)[18-20]. This variation may be due to the different vaccination schedules implemented by each country. For example, Ethiopia has not yet included the hepatitis B vaccine in its EPI, while Djibouti started immunization in 2012 and aimed to reach 85% coverage by 2019[21]. The introduction of the vaccine is not sufficient to warrant a low MTCT rate in a country. In Angola the high rate of MTCT was associated with low birth rates in health facilities and a lack of qualified staff despite the introduction of Hep B-BD.

Our results were close to those observed in Ghana (5.8% out of 454) and Cameroun (5.6% out of 607), and the small observed difference may be due to the size of the study population, the early administration of HBIG and Hep B-BD vaccines to children born to HBsAg-positive mothers in our study[22], or an intrafamilial horizontal transmission. In any case, all these values are well above the WHO target (0.1% for children under 5) and the rates observed in developed countries such as Japan (1.9%), Malaysia (2.6%), Denmark (2.3%), and in a few rare cases in southern countries such as Burkina Faso[23-26]. This difference in the prevalence of MTCT of HBV between northern and southern countries may be

Table 2 Biological status of the infants and response to immunization

Variables	Frequency	%
Infants birth weight		
< 2500 g	9	18
2500-3500 g	36	72
> 3500 g	5	10
Delivery mode		
Vaginal	39	78
Cesarean	11	12
Sex of infants		
Male	32	64
Female	18	36
HBIG + Hep B-BD vaccine		
Yes	50	100
No	0	0
Vaccination Hep B3 (penta 1, 2, 3)		
Yes	50	100
No	0	0
Response to vaccine		
< 100	33	84
≥ 100	5	16
Negative	2	NA
Immunoprophylaxis failure		
Yes	2	4
No	48	96

HBIG: Hepatitis B immunoglobulin; Hep B-BD: Hepatitis B Birth Dose; Hep B3: Pentavalent vaccine hepatitis B vaccine administered at 6 wk, 10 wk, and 14 wk of age; NA: Not available.

due to an overall lower prevalence of HBV in the general population, a well-established systematic vaccination program, improved storage conditions, and better access to health care. However, it is important to note that the situation may vary from country to country. One example is Burkina Faso where the prevalence remains at 1%.

It is also important to note that achieving a 0.1% failure rate in SSA, where HBV prevalence is over 8%, presents significant challenges. Several factors contribute to this situation, including financial and human resource constraints, a high proportion of births in rural areas, poorer quality maternity services, and the prevalence of other major health problems such as HIV/AIDS, malaria, and tuberculosis, which have often taken precedence in health priorities. According to WHO projections, the Afro region will not achieve this goal before 2100[27].

Factors associated with immunoprophylaxis failure

In our study, 2 out of 3 pregnant women with HBeAg-positive and HBV DNA viral load above 200000 IU/mL transmitted HBV to their infants. Analysis of factors associated with immunoprophylaxis failure in infants showed a significant association with HBV DNA levels and the mother's HBeAg status. These factors have been identified as reliable markers of active HBV replication and were the only factors associated with immunoprophylaxis failure in our study. Several recent meta-analyses have reported a high incidence of MTCT associated with high HBV DNA levels above 200000 IU/mL and HBeAg-positive status despite a vaccination series associated with HBIG[28,29]. These findings highlight potential targets for improving prevention strategies.

In addition, our results confirmed that combined immunoprophylaxis is effective in preventing MTCT in HBeAg-negative pregnant women, but additional measures such as peripartum prophylaxis are definitively needed for high-risk pregnant women (HBeAg positive and high viremia). Indeed, the WHO recommends that pregnant women who test positive for HBV infection (HBsAg positive) and whose HBV DNA viral load is ≥ 200000 IU/mL should receive tenofovir prophylaxis from the 28th week of pregnancy until at least delivery to prevent MTCT of HBV. It is important to note that molecular tests are the first option for stratifying at-risk pregnant women and identifying those who are eligible for

Table 3 Characteristics of two hepatitis B virus-infected children born to hepatitis B surface antigen-positive mother

Characteristics	Infant 1	Infant 2
Mother data		
Age of mother	34	32
Education level	Illiterate	Illiterate
Family history of HBV	Yes	Yes
Blood transfusion	No	No
Parity of mother	Multiparous	Large multiparous
First antenatal care	3 trimester	3 trimester
History of abortion	No	No
HBV DNA	> 200000 UI/mL	> 200000 UI/mL
HBeAg status	Positive	Positive
Infant data		
Birth weight	3.5 kg	2.5-3.5 kg
Delivery mode	Vaginal	Vaginal
Birth rank	2	3
Sex	Male	Male
HBIG + Hep B-BD	Yes	Yes
Hep B3 (penta 1,2, and 3)	Yes	Yes

HBeAg: Hepatitis B e antigen; HBIG: Hepatitis B immunoglobulin; HBV: Hepatitis B virus; Hep B-BD: Hepatitis B Birth Dose; Hep B3: Pentavalent vaccine hepatitis B vaccine administered at 6 wk, 10 wk, and 14 wk of age.

treatment. However, their widespread availability is expensive and requires high-quality laboratories, which can be a significant challenge in low-income countries. Therefore, in settings where antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative to determine eligibility for tenofovir prophylaxis to prevent MTCT of HBV [30]. A meta-analysis showed that HBeAg has a good accuracy in identifying HBV DNA levels of 5.30 Log_{10} IU/mL or greater in pregnant women with a pooled sensitivity of 88.2% (83.9%-91.5%) and pooled specificity of 92.6% (90.0%-94.5%), and a sensitivity of 99.5% (95%CI: 91.7-100) in predicting MTCT of HBV infection despite infant immunoprophylaxis[31].

Immune response

Adequate primary vaccination ensures long-term protection, and the anti-HBs titer of infants is an important indicator of whether they have immunity that could protect them from potential exposure to HBV. In this study, all infants received a planned immunoprophylaxis protocol combining HBIG + anti-HBV. The majority of infants (84%) achieved a good level of protection (> 100 mUI/mL), and eight infants showed a weak immune response (< 100 mUI/mL). Our results were closer to those obtained in China, 90% and 80%, but higher than those of Selton *et al*[32] in France who observed 68% in 60 infants exposed to HBV. Recent studies in Southeast Asia, particularly in Thailand and China, have reported a percentage of infants with 100% satisfactory seroprotection after vaccination[33,34].

In general, it is estimated that 10%-20% of infants vaccinated after birth develop a poor response to the vaccine[35,36]. Our results may depend on the choice of definition of vaccine response. In this study, we considered the achievement of seroprotection (anti-HBs < 100 mIU/mL), considered satisfactory by some authors, to be insufficient and aimed for a rate of excellent protection (anti-HBs > 100 mIU/mL). Vaccine response may also depend on the timing of the HBs antibody test in relation to the last HBV vaccine injection[37]. The eight poorly responding infants are at risk of horizontal contamination. Recommendations for this group vary in the literature, with some advocating the need for a booster dose for infants with an HBs antibody titer less than 10 mIU/mL at 12 mo[38,39].

Factors associated with vaccine response

Nevertheless, few studies focused on the risk factors related to anti-HBs titers under 100 mIU/mL. In our study, only birth weight < 2500 g was an independent predictor of poor response. Indeed, birth weight tended to be lower in poor responders (< 2500 g) than in good responders (2500-3500 g). The difference was statistically significant (P < 0.010), contrary to the data of some authors probably due to insufficient numbers [Linder *et al*[37] (n = 137) and Losonsky *et al* [40] (n = 147)]. Low birth weight is not a contraindication to vaccination. However, some low-birth-weight infants with clinical instability may not respond as well to the Hep B-BD vaccine as full-term or normal-weight infants. In this case,

Table 4 Analysis of risk factors for failure of immunoprophylaxis

Variables	No failure, *n* = 48	Failure, *n* = 2	χ^2	*P* value	OR (95%CI)	*P* value
HBV DNA of mother			32.64	< 0.001		
> 200000 IU/mL	1 (2.1)	2 (100)			Reference	
< 200000 IU/mL	47 (97.9)	0 (0)		-	158.00 (5.05-49.80)	0.004
Mother HBeAg status			32.64	< 0.001		
Negative	47 (97.9)	0 (0)			Reference	
Positive	1 (2.1)	2 (100)		-	158.00 (5.05-49.80)	0.004
Family history of HBV			1.07	0.300		
No	31 (65.0)	2 (100)			Reference	
Yes	17 (35.0)	0 (0)		-	0.36 (0.20-198.00)	0.517
History of abortion			0.89	0.340		
No	33 (69.0)	2 (100)			Reference	
Yes	15 (31.0)	0 (0)		-	0.43 (0.02-9.55)	0.595
Delivery mode in infants			0.59	0.440		
Vaginal	37 (77.0)	2 (100)			Reference	
Cesarean	11 (23.0)	0 (0)		-	1.50 (0.06-34.00)	0.780
Parity of mother			0.93	0.630		
Null parous	7 (15.0)	0 (0)			Reference	
Multiparous	30 (62.0)	1 (50.0)		-	0.73 (0.27-19.00)	0.181
Large multiparous	11 (23.0)	1 (50.0)		-	1.95 (0.07-54.00)	0.693
Infant birth weight			1.53	0.460		
2.5-3.5 kg	35 (73.0)	1 (50.0)			Reference	
< 2.5 kg	8 (17.0)	1 (50.0)		-	4.37 (0.25-77.65)	0.315
> 3.5 kg	5 (10.0)	0 (0)		-	2.15 (0.08-59.70)	0.651
Infant sex			1.17	0.280		
Male	30 (62.0)	2 (100)			Reference	
Female	18 (38.0)	0 (0)		-	0.54 (0.12-2.49)	0.428
Blood transfusion			0.50	0.490		
No	35 (73.0)	1 (50.0)			Reference	
Yes	13 (27.0)	1 (50.0)		-	2.69 (0.16-46.00)	0.495
First antenatal care of mother			3.70	0.157		
1 trimester	16 (33.0)	0 (0)			Reference	
2 trimester	16 (33.0)	0 (0)		-	0.02-53.40	1.000
3 trimester	16 (33.0)	2 (100)		-	5 (0.22-112.00)	0.310

Data are *n* (%). CI: Confidence interval; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; OR: Odds ratio.

Hep B-BD may be delayed until the neonate is 1 mo old[41]. It is essential to pay particular attention to low-birth-weight infants for anti-HBs levels, and booster vaccinations against hepatitis B should also be considered if necessary.

Limitations

This study was not specifically designed to compare the efficacy of the hepatitis B vaccine alone with a combination of HBIG and anti-HBV vaccine. Nevertheless, further studies will be needed to evaluate this observation. It is also difficult to know whether children who tested positive for HBV were infected vertically at birth or horizontally during infancy. Finally, the optimal dose of HBIG in our context or the ideal time to administer the first dose of vaccine at birth was not evaluated.

Table 5 Risk factor analysis for low immune responses

Variable	AcHBs Vt ≥ 100 mUI/mL	AcHBs Vt < 100 mUI/mL[1]	χ^2	*P* value	OR (95%CI)	*P* value
HBV DNA			0.20	0.650		
> 200000 IU/mL	1 (2.5)	0 (0)			Reference	0.794
< 200000 IU/mL	39 (97.5)	8 (100)		-	1.54 (0.05-41.38)	
HBeAg status			0.20	0.650		
Negative	39 (97.5)	8 (100)			Reference	
Positive	1 (2.5)	0 (0)		-	1.54 (0.05-41.38)	0.794
Antecedent HBV			0.46	0.500		
No	25 (62.0)	6 (75.0)			Reference	
Yes	15 (38.0)	2 (25.0)		-	0.56 (0.10-3.11)	0.504
History of abortion			4.36	0.370		
No	25 (62.0)	8 (100)			Reference	
Yes	15 (38.0)	0 (0)		-	0.09 (0.01-1.79)	0.117
Mode of delivery			0.59	0.440		
Cesarean	10 (25.0)	1 (12.0)			Reference	
Vaginal	30 (75.0)	7 (88.0)		-	2.33 (0.25-21.36)	0.453
Birth weight in kg			17.97	< 0.001		
2.5-3.5	34 (85.0)	1 (12.0)			Reference	
< 2.5	4 (10.0)	4 (50.0)		-	34 (3.01-383.86)	0.004
> 3.5	2 (5.0)	3 (38.0)		-	51 (3.51-740.17)	0.004
Infant sex			1.17	0.420		
Male	26 (65.0)	4 (50.0)			Reference	
Female	14 (35.0)	4 (50.0)		-	0.54 (0.12-2.49)	0.428

Data are *n* (%).

[1]Low immune response. AcHBs: Hepatitis B surface antibody; CI: Confidence interval; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; OR: Odds ratio; Vt: Viral titer.

CONCLUSION

Our study showed that the combination of Hep B-BD and HBIG provided protection against MTCT of HBV, although the results remain above WHO targets. It also highlighted the importance of a national HBV policy that could implement WHO recommendations, such as the introduction of peripartum antiviral prophylaxis for women at risk, which is a strategy more financially feasible than HBIG. This policy should also recommend HBeAg as an alternative to molecular testing for identifying pregnant women eligible for treatment.

FOOTNOTES

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